CASE REPORTS

Approach to Diagnosis and Treatment of Herpes Simplex Encephalitis

A Report of Two Cases

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ENCEPHALITIS DUE TO INFECTION with herpes simplex (Herpesvirus hominis) has been described as the most common cause of sporadic fatal encephalitis.[1] Herpes simplex virus was first isolated in encephalitis in 1941 from the brain of a week-old infant in whom type A intranuclear inclusion bodies were noted post-mortem.[2] Herpes simplex has subsequently been recognized as being frequently associated with acute necrotizing encephalitis,[3] and it can present clinically as a "temporal lobe" syndrome[4] or as an intracranial mass lesion.[5] Improved methods of laboratory diagnosis have contributed to the early diagnosis of the clinical syndrome of herpes encephalitis. The increasing use of brain biopsy has made possible the diagnosis of

herpes encephalitis in living patients, by typical histological appearance, by specific immuno-fluorescence for herpes antigen, or by isolation of the virus from the biopsy specimen. A new method of making immediate serological diagnosis of herpes infection from a single specimen has also been proposed.[6] Although cerebro-spinal fluid (CSF) has proved a poor source[7] for the isolation of herpes simplex, diagnosis by immunofluorescence for herpes simplex in CSF has been reported twice.[8,9]

The use of iododeoxyuridine (IDUR), a thymidine analogue shown to have in vitro activity against herpes simplex.[10] was first reported in herpes encephalitis by Breeden et al in 1966[11] and has been used many times since. The use of IDUR in herpes encephalitis is now accepted, although its efficacy has not been proved by controlled trial.[1] It has been felt to be efficacious by investigators evaluating it on the basis of clinical improvement and elimination of virus shedding in individual cases and by comparison of the outcome of treated cases with previous untreated cases.

The purpose of this communication is to report two additional cases of herpes encephalitis recently seen in consultation by our group. A review of herpes encephalitis suggested an improved survival in herpes simplex encephalitis treated with IDUR, as compared with previously untreated cases. On the basis of this analysis of the literature, it seemed appropriate to treat apparent herpes encephalitis with iododeoxyuridine, after steps leading to specific viral diagnosis, including open brain biopsy, were begun.

Reports of Cases

Case 1. A previously healthy 22-year-old white man had sudden development of behavioral changes characterized by inability to work and failure to recognize people. He became with-

drawn, stared into space, had visual hallucinations, and spoke in brief sentences out of context. Three weeks previously he had had a cold sore on his lip which he picked until it bled; and for one week he had had symptoms of an upper respiratory infection. On the second and third days of this illness he became febrile and had an earache, for which he received a penicillin injection. On the fifth day of illness he had a grand mal seizure and was admitted to the hospital where temperature of 40°C and nuchal rigidity were noted. Bilateral injection of tympanic membranes was observed. On neurologic examination a questionable mild right central facial paresis was noted, and Hoffmann's sign was present on the right side. Altered sensorium and behavior were observed also. The patient lay on his left side and did not respond to verbal stimuli; he did not speak except for periodic outbursts of profanity. At times he had tonic deviation of his eyes to the right, and focal temporal seizures were suspected. On lumbar puncture the csf was cloudy with 346 white blood cells per cu mm—80 percent lymphocytes and 20 percent polymorphonuclear cells. Protein content was of 100 mg and glucose content 88 mg per 100 ml. A brain scan showed minimal findings in the left inferior frontotemporal region. An electroencephalogram showed focal slowing and spikes from the left frontotemporal electrodes. Administration of diphenylhydantoin (Dilantin®) and phenobarbital was begun but intravenous diazepam (Valium®) was necessary for control of agitated behavior. Dexamethasone also was given, 4.0 mg four times a day. On the fourth day in hospital (eight days after onset) the patient's condition suddenly deteriorated; he had right hemiparesis, a dilated unreactive pupil and unresponsiveness to deep pain stimuli. Other transient cranial nerve signs suggested impending herniation. Brain scan and left carotid arteriogram suggested a mass on its left. On craniotomy congestion and swelling of the brain was noted and there were several areas of necrosis in the left frontotemporal region. Exploration failed to reveal an abscess, and cerebral biopsy specimens were obtained. A wide decompression and grafting of the dura were performed to relieve the cerebral swelling. Microscopic sections revealed typical necrotizing encephalitis and many intranuclear inclusions.

The brain biopsy specimen was processed for specific immunofluorescence at the California State Public Health Viral and Rickettsial Laboratory. The report that the biopsy specimen was strongly positive for herpes simplex was received the same day. On the following day (ninth day of illness) IDUR was started at a dose of 100 mg per kilogram of body weight per 24 hours in a continuous intravenous infusion that was continued for five days. The patient remained comatose for 48 hours after decompression and 27 hours after IDUR was started, after which time he opened his eyes, followed objects and moved all extremities; however, the right arm moved less than the left. His neck was supple, pupils were equal and reactive, and he was responsive to painful stimuli and commands. On the eighth hospital day, evidence of a cerebral salt-wasting syndrome appeared, with serum sodium of 124 mEq, serum chloride of 82 mEq and 24-hour urine sodium excretion of 439 mEq per liter. He was treated with salt and restriction of fluid.

On the tenth hospital day signs of pneumonia appeared. Staphylococcus aureus resistant to penicillin was recovered on deep endotracheal suction. Treatment with methicillin resulted in resolution of clinical and radiologic signs by the fourteenth day. On this day, one day after cessation of IDUR, signs of bone marrow depression occurred. Maximal depression of platelets (23,-000 per cu mm), hemoglobin (7.46 gm per 100 ml) and white blood cell counts (3,800 per cu mm) followed on the fourth, fifth and sixth days after cessation of IDUR.

There was slow but steady improvement of neurological and mental status despite the above complications. Twelve days, 19 days and 26 days respectively after initiation of IDUR therapy, the patient was able to feed himself, to walk with assistance and to speak simple words. By the twenty-sixth day neurological evaluation was negative except for mild right central facial paresis and severe receptive and expressive aphasia. Twelve months later he still had severe expressive aphasia and possible memory defect for remote learning, making a protected environment necessary.

Infection with herpes simplex was confirmed by isolation of the virus from the brain biopsy specimen. Serum specimens obtained on the sixth, twenty-fifth and fifty-first days of illness

showed conventional neutralizing antibody titers against herpes simplex of less than 1:8, 1:32, and 1:64. These same specimens showed complement-requiring neutralizing antibody titers of 1:32, 1:64, and 1:256.

Case 2. A 34-year-old white woman was admitted to the psychiatric ward of the Stanford University Hospital because of agitation, disorientation and auditory and visual hallucinations of several days' duration. Five days before admission she had had a four-day illness consisting of fever and cough, which had been treated with ampicillin. On the third hospital day mild nuchal rigidity and increased tone were noted, without focal neurological findings. The temperature was 37.5 C; other vital signs were normal. Leukocytes numbered 12,500 per cu mm of blood, with the cell differential within normal range. On lumbar puncture the opening pressure was 270 mm (water) and the CSF was clear. It contained seven leukocytes (1 polymorphonuclear) and 136 erythrocytes per cu mm, glucose 43 mg and protein 171 mg per ml. Bacterial, fungal and mycobacterial cultures, Gram-stain and India ink preparations were negative. A brain scan was normal. The electroencephalogram showed diffuse slowing. Two days later the CSF showed 120 leukocytes and 50 erythrocytes per cu mm and glucose of 30 mg per 100 ml. Blood glucose was 80 mg per 100 ml. The patient remained confused, and had right-sided movements that were interpreted as myoclonic jerks for which Dilantin® was given. The next day (seventh hospital day) she had continuous mouth and jaw movements. An EEG showed a subcortical left temporal focus. The patient was no longer responsive, this believed to be secondary to status epilepticus. Because of the low CSF glucose, administration of ampicillin, isoniazid and streptomycin was begun. On the eighth hospital day she was completely comatose. A brain biopsy specimen was obtained and decompression was carried out. Hemorrhagic inflammation was noted grossly. Histological sections showed inflammation without inclusion bodies. Immunofluorescence for Herpesvirus hominis was negative. The patient received IDUR, 40 mg per kg of body weight, in a continuous intravenous infusion over the next 24 hours. On the tenth hospital day, a full supply of IDUR was obtained, and she then received 100 mg per kg per 24 hours for five days.

Following the surgical procedure and during the IDUR therapy, she remained completely comatose. The postoperative course was complicated by Group A streptococcal bacteremia, bilateral pulmonary infiltrates felt to be pulmonary hemorrhages, and gastrointestinal bleeding. She died of bronchopneumonia on the fortieth hospital day without ever regaining consciousness. Thrombocytopenia and leukopenia were first noted on the fourth day following the cessation of IDUR therapy, and an abnormal serum glutamic oxaloacetic transaminase (SGOT) and bilirubin on the sixth day. The nadir of bone marrow depression occurred on the eighth day after cessation of IDUR. At that time the platelets were 12,000 per cu mm and there was evidence of gastrointestinal and intrapulmonary bleeding. The peak abnormality in liver functions also occurred at this time, with bilirubin of 3.0 mg per 100 ml of blood. The leukocyte count was never lower than 3,800 per cu mm.

Infection with herpes simplex was suggested by a rise in complement-fixing antibody titer from 1:16 on the seventh and tenth day of illness to 1:128 on the thirty-ninth day of illness. There was also a four-fold difference in conventional neutralizing antibody (less than 1:8) and complement-requiring neutralizing antibody (1:32) on the specimen drawn on day seven. Viral cultures of the brain biopsy specimen in the Virus Diagnostic Laboratory of Stanford University Hospital after several blind passages grew a virus identified by immunofluorescence and neutralization as herpes simplex. Viral cultures of postmortem brain and lung tissue were negative and no intranuclear inclusion bodies were noted in neuropathologic examination.

Discussion

The diagnosis of herpes encephalitis can be suspected on clinical grounds. In this country, acute febrile encephalitis without an associated immunization, infectious disease or epidemiological evidence of arborvirus infection is highly suggestive of herpes encephalitis. Organic psychosis, focal neurological signs, especially those of temporal lobe origin, or signs of a mass lesion are typical of herpes encephalitis. Often the presence of a mass lesion is demonstrated preoperatively, as in our first patient, by angiography or brain scan.

TABLE 1.—*Mortality of "Untreated" Herpes Encephalitis*

Reference	Overall mortality		Comatose patients		Non-comatose patients	
Drachman et al (4)	3/6	(50%)	1/2	(50%)	1/6	(17%)
Lieder et al (15)	4/15	(27%)	3/9	(33%)	2/4	(50%)
Miller et al (16)	10/20	(50%)	10/13	(77%)	0/7	(0%)
Olson et al (7)	25/36	(70%)	24/30	(80%)	1/6	(17%)
Nolan et al (13)	3/7	(43%)	3/4	(75%)	0/3	(0%)
Meyer et al (17)	5/13	(38%)	—		—	
Miller, Ross (18)	5/11	(46%)	—		—	
	55/108	(51%)	41/58	(71%)	4/26	(15%)

Herpes encephalitis, when suspected, may rapidly be confirmed in some cases by brain biopsy. When positive, specific immunofluorescence showing the presence of the herpes antigen in brain tissue can confirm the diagnosis the day of the biopsy, as in our first patient and one other reported patient[12], though the frequency of false negatives by immunofluorescence, as occurred in our second case, is not yet known. The finding of intranuclear inclusion bodies in a brain biopsy can also yield an immediate presumptive diagnosis. However, intranuclear inclusions are frequently absent. For example, in five patients with serological evidence of herpes encephalitis, Nolan et al found inclusions in only one of the five biopsy specimens.[13] Finally, rapid diagnosis of herpes encephalitis might be made by finding herpes-like particles in electron micrographs of touch preparations of the brain biopsy. Such preparations could be made the same day, and have been reported to be of value in other viral syndromes.[14]

Isolation of the virus from CFS or brain biopsy specimens permits definitive diagnosis, but several days may be required for the virus to be detected in tissue culture. Serological confirmation of herpes infection by a fourfold rise in either neutralizing or complement-fixing antibody may not always be noted and is rarely useful in acute situations. Frequently the patient already has a high-titer of antibody when first seen, precluding the detection of an antibody rise. Recently, Lerner et al reported that the diagnosis of herpes infection could be made from a single serum specimen, by the finding of fourfold higher levels of complement-requiring neutralizing antibody compared with conventional neutralizing antibody,[6] but this has not yet been confirmed by other investigators. Even this method has an inherent delay of 24 to 36 hours.

The diagnosis of herpes encephalitis in both of our patients was suspected on clinical grounds. Open brain biopsy helped establish the diagnosis within 12 hours in one patient by means of positive immunofluorescence. In the other patient, open brain biopsy was immediately helpful only in that it helped rule out other infectious causes of encephalitis. In both cases, serological rise in complement fixing antibody helped confirm infection with herpes simplex, as did viral isolation. Isolation of the virus in the second case, however, required several blind passages. Herpes simplex was not isolated from a part of the same specimen that was sent to the State Laboratory, suggesting an advantage of having available a hospital based viral diagnostic laboratory where cultures can be pursued with clinical insights. The initial serum specimens taken on the sixth day of illness (Case 1) and on the seventh day of illness (Case 2) were suggestive of herpes simplex infection by the ratio of complement-requiring to conventional neutralizing antibodies.

Data on mortality and incidence of permanent neurologic sequelae following untreated herpes encephalitis vary[4,7,13,15-18] (Table 1). There are also many individual case reports of fatal cases, though Pierce et al reported two severe cases with survival, and MacCallum one case.[5,19] The overall mortality of untreated herpes encephalitis in the seven reports summarized in Table 1 was 51 percent (55 of 108) and the range was

from 27 percent to 70 percent. The mortality for patients with coma was 71 percent (41 of 58), compared with only 15 percent (4 of 26) for those who did not have coma. Since five of the seven reported series[7,13,15-18] deal with retrospective analysis of cases searched out by a central reference laboratory, the patients had been treated in diverse hospitals. The method of diagnosis of herpes infection varied widely, being based in some cases only on a rise in antibody titer, although most of the fatal cases were confirmed by isolation of the virus at postmortem examination.

The possibility of using IDUR in the treatment of herpes encephalitis was suggested by the *in vitro* finding that IDUR inhibits a variety of DNA viruses, including herpes simplex, most likely acting as a thymidine analogue and interfering with the synthesis of viral DNA.[10] Experimental animal and clinical data confirmed its efficacy in keratitis due to herpes simplex,[20] and it has become an accepted mode of therapy for this condition. IDUR was first used systematically in compromised hosts with severe disseminated vaccinia and varicella-zoster infections.[10] Its use in systemic infection with cytomegalovirus (CMV) has also been reported.[21] Its use has also been reported in an immunosuppressed patient who received the drug locally and systemically, without apparent benefit, for widespread ulcerating cutaneous and mucosal herpetic lesions.[22]

We have attempted to summarize all the published cases of IDUR-treated herpes encephalitis, excluding only neonatal infections (Table 2).[11-13,23-29] The overall mortality among the IDUR-treated patients with coma was 29 percent (5 of 17), while one of three patients without coma died. Seven of the 14 surviving patients made full recovery, while the rest were left with moderate or severe neurological deficits. The 29 percent mortality observed in the IDUR-treated patients with coma compares favorably with the 54 percent overall mortality and 71 percent mortality of comatose patients observed in the symptomatically treated group.

Herpes encephalitis in newborn infants, particularly prematures, is often a disseminated infection, rather than only encephalitis as in adults, involving the skin and many viscera as well as the CNS, and it carries perhaps an even worse prognosis. It is almost always owing to primary infection, acquired either transplacentally or at the time of delivery.[30] It may more often be due to herpes simplex type II, which has been said to be more resistant to IDUR. Cases of neonatal herpes infection treated with IDUR have been grouped separately (Table 3).[9,31-33] Only two of seven patients died, though a third died six months later of pneumonia. However, only one of these seven patients was felt to be "normal" following recovery from the infection. One patient was treated twice—he improved following IDUR therapy on the tenth day of illness, but then had a clinical and virological relapse, with herpes again found in the CSF. He was again treated with IDUR, and then the virus was successfully eradicated, though he had evidence of hydranencephaly at age 12 months.[9]

The efficacy of IDUR in herpes encephalitis is suggested both by the lowered mortality found when the treated cases, as a whole, are compared with the previously published experience, and by the course of the illness described in many of the cases, wherein improvement seemed temporally related to the use of IDUR. In a disease such as viral encephalitis, one would expect that early treatment might be much more likely to bring benefit than treatment initiated late in the disease, where damage to brain cells caused both by viral replication and brain swelling is likely to be permanent. A trend favoring earlier treatment is not, however, apparent from the summarized data in Table 2, suggesting either that treatment may not have affected outcome, or that the more indolent cases, diagnosed and treated later in the course of disease, have a better prognosis. Although the improved outcome in the IDUR-treated cases suggests that IDUR may have been of benefit in herpes encephalitis, there are many other factors that might account for this difference in outcome. "Symptomatic" care of encephalitis may have been quite different in one medical center than in another, and may have improved overall in the time period when IDUR was used. Surgical decompression procedures may have been more common among the IDUR-treated cases, possibly because of increased recognition of herpes encephalitis as causing a mass lesion, or because of more vigorous attempts to make a specific diagnosis.

Most patients have had signs of toxicity related to IDUR, including jaundice, other liver function abnormalities, bone marrow depression, stomatitis, and alopecia. Bone marrow depression oc-

TABLE 2.—*Summary of Reported IDUR-Treated Cases of Herpes Encephalitis*

Author and reference	Age (yr)	Sex	Coma present (HD)*	Mass lesion present	Focal Neurological signs	IDUR Dosage			Side effects	Surgical decompression or biopsy (HD)	Outcome	Means by which diagnosis established
						Day started after first symptom	HD begun	Total dose mg/kg				
Breeden et al (11) [Page et al (23)]	34	M	+(7)	+Art +Scan +EEG	+	10	8	550	↓WBC ↓RBC ↓Platelets Stomatitis Abnormal liver function tests	Bx 5 7 8	Recovery Minimal neurological signs	Isolation (Bx) Serology (Neut)
Buckley, MacCullum (24)	41	F	−	−Art −PEG −EEG	+	21	5	14	None	2	Quadriparetic, dysphasic	Isolation (Bx) Serology (Neut, CF)
Evans et al (25)	8	F	+(5)	+EEG	+	55	53	500	None	53	Hemiplegic Mental retardation	Isolation (Bx) Serology (CF)
Marshall (8)	13	M	+(10)	+EEG +Art	+	10	10	200	↓WBC	8 10	Recovery Minimal neurological signs	Fluorescent Ab on CSF, venous blood Isolation (Bx) Serology (CF)
Bellanti et al (26)	1	F	+(1)	+EEG	−	13	13	600	Abnormal liver function tests Hepatomegaly	5 20	Recovery Moderate spasticity	Isolation (Bx) Serology (CF)
Dayan, Lewis (27)	60	M	+	?	+	?	?	?	Cholestatic jaundice	5	Died	Isolation (Bx)
Silk, Roome (12)	6	M	+(4)	?	+	6	6	550	Abnormal liver function tests Alopecia	Bx	Aphasic, hemiplegic, incontinent, retarded	Immunofluorescence (Bx) Isolation (Bx) Serology (CF) Serology (CF)
Nolan et al (13) [Meyer et al (28)]	57	F	+(4)	+EEG −Art	+	13	10	430	(died)	Bx	Died	Isolation (Bx, PM) Inclusion bodies (Bx, PM) Serology (CF, Neut, CF-neut)
	24	F	+(6)	+EEG −Art	+	13	6	430	Stomatitis ↓WBC ↓RBC ↓Platelets Alopecia	—	Recovered	Serology (CF, Neut, CF-neut)
	22	F	−	+Scan −EEG	−	14	6	430	Stomatitis ↓WBC ↓RBC ↓Platelets Alopecia	—	Recovered	Serology (CF, Neut, CF-neut)

Age	Sex		Procedures		Onset (days)	Duration (days)	Dose	Toxicity		Outcome	Diagnosis
10	M	+(1)	+Scan -EEG	+	9	2	450	Stomatitis ↓WBC Alopecia	2	Recovered	Serology (CF, CF-Neut)
16	F	+(1)	+EEG -PEG	–	3	?	450	Stomatitis ↓WBC ↓Platelets Alopecia	Bx	Recovered	Serology (CF, Neut, CF-Neut)
62	F	–	-Art +EEG	+	6	3	100	(died)	Bx	Died	Isolation (Bx, Pm) Serology (CF, Neut)
Rappel et al (29)											
58	M	+	+EEG +Art -Scan	+	16	?	500	"Transient hepatic toxicity and bone marrow depression"	9	Died	Isolation (Bx) Serology (CF) Inclusions (Bx, PM)
12	F	+	+EEG +Art	+	16	?	320	None	16	Recovered	Serology (CF)
56	M	+	+EEG	–	27	?	500	"Transient....." Alopecia	27	Recovered, impaired mental capacity	Serology (CF)
45	F	+	+EEG +Art +Scan +PEG	+	18	?	500	"Transient....."	—	Recovered Moderate memory defect Slight aphasia	Serology (CF)
65	F	+	+EEG +PEG -Art	+	9	5	500	"Transient....."	9	Died	Electron micrography
Our patients											
22	M	+(8)	+EEG +Scan +Art	+	9	5	500	↓WBC ↓Platelets ↓RBC	8	Aphasia	Immunofluorescence (Bx) Isolation (Bx) Serology (Neut, CF-Neut)
35	F	+(4)	+EEG -Scan	–	6	6	500	↓WBC ↓Platelets ↓RBC ↑SGOT ↑Bilirubin	6	Died	Serology (CF, CF-Neut) Isolation (Bx)
TOTALS: 1-65 yr	F-12 M-8	17/20	15/18 +EEG 5/7 +Scan 5/11 +Art 2/4 +PEG	15/20	6-55 days	2-53 days	320-500	5/18 Stomatitis 12/18 Bone marrow depression 9/18 Abnormal liver function tests 6/18 Alopecia	17/20 Bx and/or decompression	6/20 Died 7/20 Recovery, moderate or severe residua 7/20 Recovery, minimal or no residua	12/20 Isolation 18/20 Serology 3/20 Immunofluorescence 1/20 Electron micrography

NOTES:
*HD = Hospital Day
Art. = Caroid Artiogram
Scan = Radioactive brain scan
PEG = Pneumoencephalogram
Bx = Biopsy
PM = Post-mortem

CF = Complement fixing antibody
Neut = Neutralizing antibody
CF-Neut = Ratio of complement-requiring neutralizing antibody to conventional neutralizing antibody

TABLE 3.—*Summary of Reported IDUR-Treated Cases of Herpes Encephalitis in Neonates*

Reference	Age,* Sex	Total Dose IDUR	Other Organ Involvement	Side effects	Outcome	Means by which diagnosis established
Partridge, Millis (31)	4 days, FT,** F	580 mg/kg	Skin, ? Heart, ? Lungs	None	Died. (Improved following IDUR, but relapsed 5 days later)	Isolation (vesicles, nose and throat swabs)
Golden et al (9)	4 days, P,*** M	1000 mg/kg (two 500 mg/kg courses, 23 days apart)	Eyes, Skin	WBC, Platelets, RBC	Retarded. (Improved following first course of treatment, but relapsed with virus re-isolated from CSF)	Isolation (CSF, vesicles, throat swabs) Immunofluorescence (CSF)
Tuffli, Nahmias (32)	7 days, P, F	200 mg/kg	Eyes, Skin	WBC	Retarded. Died age 6 months	Isolation (HVH II)**** (vesicle, eyes, throat)
	14 days, P, M	250 mg/kg	Skin	"Aphthous stomatitis"	Well, recurrent herpes infection	Isolation (HVH II) (Skin) serology
AJN (reported in Reference 32)	Infant, P	200 mg/kg	Skin, Viscera	?	Died	Isolation (HVH II) (brain, liver)
Wenzel (reported in Reference 32)	3-month infant	250 mg/kg 10 mg/kg intrathecally	?	?	Mild hemiparesis	?
Charnock, Cramblett (33)	11 day, FT, F	410 mg/kg	Skin	Platelets	Impaired	Isolation (skin, brain bx)

NOTES: *Age when first evidence of herpes infection appeared **FT=Full term ***P=Premature ****HVH II=*Herpesvirus hominis* Type II

curs usually after cessation of therapy, and it may be severe, as it was in our second case where the resultant thrombocytopenia was considered responsible for the pulmonary and gastrointestinal hemorrhages that complicated the post-treatment course.

The establishment of the efficacy of IDUR in herpes encephalitis by means of controlled trials seems mandatory before IDUR therapy can be considered generally accepted for this condition. The premature acceptance of IDUR would commit to treatment patients with herpes encephalitis in spite of the potentially serious toxicity associated with this agent, and it also might preclude the experimental use of other (possibly more effective) antiviral drugs. The fact that not enough cases of herpes encephalitis are seen at any one center to permit any kind of valid controlled trial has been recognized. A large double-blind trial, involving eight to twelve medical centers is currently being planned.

There are other situations in which systemic IDUR has been and can be used. Severe life-threatening local and disseminated herpes infection has been noted in a variety of "compromised" hosts; in premature infants, patients with gross malnutrition, severe burns or eczema, immunosuppressed transplant recipients or patients with cellular immune defects.[34] All such infected patients are also potential candidates for antiviral therapy. Furthermore, immunosuppressed patients and patients with leukemia or lymphomas are also known to have a higher incidence of severe infections with other DNA viruses such as varicella-zoster, cytomegalovirus, and vaccinia. Such patients have also been treated in the past with IDUR or other thymidine analogues, cytosine arabinoside, isatin-B-methylthiosemicarbazone, and polycytidylic-inosinic acid, an interferon inducer.[35] If the use of these antiviral drugs is going to be considered, it would seem important that they be used as early as possible in the course of the severe viral infection, rather than as a desperation measure in an already dying patient. Early diagnosis and specific treatment will require (1) an awareness of the clinical syndromes produced by these viruses. (2) a willingness to use aggressive means of diagnosis as soon as a life-threatening viral infection is suspected, such as brain biopsy in suspected herpes encephalitis and liver or lung biopsy in suspected CMV infections, and (3) a rapid, even if provisional,

means of specific diagnosis, including immunofluorescence and electron micrography of such biopsy material.

Summary

Because of our analysis of reported cases of herpes encephalitis, it appeared appropriate to treat two patients with herpes simplex encephalitis with iododeoxyuridine, after appropriate diagnostic steps were begun. Diagnosis was established with open brain biopsy in one patient within 12 hours, by means of specific immunofluorescence, whereas in the other patient immunofluorescent study of biopsy material was negative and the virus was only demonstrated after several blind passages of biopsy material. This report is presented to illustrate our approach to specific diagnosis and attempted treatment of significant virus infection in man.

REFERENCES

1. Hanshaw JB: Idoxuridine in herpes virus encephalitis. N Engl J Med 282:47, 1970
2. Smith MG, Lenette EM, Reames HR: Isolation of the virus of herpes simplex and the demonstration of intranuclear inclusions in a case of acute encephalitis. Am J Path 17:55-68, 1941
3. Adam JH, Jenett WB: Acute necrotizing encephalitis: A problem in diagnosis. J Neurol Neurosurg Psychiat 30:248-260, 1967
4. Drachman DA, Adams RD: Herpes simplex and acute inclusion-body encephalitis. Arch Neurol (Chicago) 7:45-63, 1962
5. Pierce NF, Portnoy B, Leeds NE, et al: Encephalitis associated with herpes simplex infection presenting as a temporal-lobe mass. Neurology 14:708-713, 1964
6. Lerner AM, Bailey EJ, Nolan DC: Complement-requiring neutralizing antibodies in encephalitis caused by Herpesvirus hominis. J Immun 104:607-615, 1970
7. Olson LC, Buescher EL, Artenstein MS, et al: Herpes virus-infections of the human central nervous system. N Engl J Med 277:1271-1277, 1967
8. Marshall WJS: Herpes simplex encephalitis treated with idoxuridine and external decompression. Lancet 2:579-580, 1967
9. Golden B, Bell WE, McKee AP: Disseminated herpes simplex with encephalitis in a neonate: Treatment with idoxuridine. JAMA 209:1218-1222, 1969
10. Calabresi P: Clinical studies with systemic administration of antimetabolites of pyrimidine nucleosides in viral infections. Ann NY Acad Sci 130:192-207, 1965

11. Breeden CJ, Hall TC, Tyler HR: Herpes simplex encephalitis treated with systemic 5-iodo-2'deoxyuridine. Ann Intern Med 65:1050-1056, 1966
12. Silk BR, Roome APCH: Herpes encephalitis treated with intravenous idoxuridine. Lancet 1:411-412, 1970
13. Nolan DC, Carruthers MM, Lerner AM: Herpesvirus hominis encephalitis in Michigan—Report of thirteen cases, including six treated with idoxuridine. N Engl J Med 282:10-13, 1970
14. Doane FW, Anderson N, Chatiyanonda K, et al: Rapid laboratory diagnosis of paramyxovirus infections by electron microscopy. Lancet 2:751-753, 1967
15. Leider W, Magoffin RL, Lennette EH, et al: Herpes simplex virus encephalitis: Its possible association with reactivated latent infection. N Engl J Med 273:341-347, 1963
16. Miller JK, Hesser F, Tompkins VN: Herpes simplex encephalitis: Report of 20 cases. Ann Intern Med 64:92-103, 1966
17. Meyer HM, Johnson RT, Crawford IP, et al: Central nervous system syndromes of "viral" etiology—A study of 713 cases. Am J Med 29:334-347, 1960
18. Miller JD, Ross CA: Encephalitis—A four-year study. Lancet 1:1121-1126, 1968
19. MacCullum FO, Potter JM, Edwards DH: Early diagnosis of herpes simplex encephalitis by brain biopsy. Lancet 2:332-334, 1964
20. Maxwell E: Treatment of herpes keratitis with 5-iodo-2'deoxyuridine (IDU)—A clinical evaluation of 1500 cases. Am J Opthal 56:571-573, 1963
21. Conchie AF, Barton BW, Tobin JO: Congenital cytomegalovirus infection treated with idoxuridine. Br Med J 4:162-163, 1968
22. Montgomerie TZ, Becroft DMO, Croxson MC, et al: Herpes simplex virus infection after renal transplantation. Lancet 2:867-871, 1970
23. Page LK, Tyler HR, Shillito T: Neurosurgical experiences with herpes simplex encephalitis. J Neurosurg 27:346-352, 1967
24. Buckley TF, MacCallum FO: Herpes simplex virus encephalitis treated with idoxuridine. Br Med J 2:419-420, 1967
25. Evans AD, Gray OP, Miller MH, et al: Herpes simplex encephalitis treated with intravenous idoxuridine. Br Med J 2:407-410, 1967
26. Bellanti JA, Guin GH, Grassi RM, et al: Herpes simplex encephalitis: Brain biopsy and treatment with 5-iodo-2'deoxyuridine. J Pediat 72:266-275, 1968
27. Dayan AD, Lewis PD: Idoxuridine and jaundice. Lancet 2:1073, 1969
28. Meyer JS, Bauer RB, Rivera-Olmos VM, et al: Neurological manifestations and use of idoxuridine in Herpesvirus hominis encephalitis. Arch Neurol 23:438-450, 1970
29. Rappel MM, Dubois D, Sprecher S, et al: Diagnosis and treatment of herpes encephalitis—A multidisciplinary report. J Neurological Sci. In press
30. Nahmias AJ, Josey WE, Naib ZM: Neonatal herpes simplex infection: Role of genital infection in mother as the source of virus in the newborn. JAMA 199:164-168, 1967
31. Partridge JW, Millis RR: Systemic herpes simplex infection in a newborn treated with intravenous idoxuridine. Arch Dis Child 43:377-381, 1968
32. Tuffli GA, Nahmias AJ: Neonatal herpetic infection—Report of two premature infants treated with systemic use of idoxuridine. Am J Dis Child 118:909-914, 1968
33. Charnock FL, Cramblett HG: 5-iodo-2'deoxyuridine in neonatal Herpesvirus hominis encephalitis. J Pediat 76:459-463, 1970
34. Nahmias AJ: Disseminated herpes simplex virus infections. N Engl J Med 282:684-685, 1970
35. Hermann EC, Stinebring WR (Eds): Second Conference on Antiviral Substances. Ann NY Acad Sci 173:1-844, 1970